REMARKS

Applicants wish to thank the Examiner for careful consideration of this application. Currently, claims 1, 4-6, 9-10, 16, and 19 are pending and claims 92-96 have been added. Claims 2-3, 7-8, 11-15, 17-18, and 20-91 have been canceled. Each of the objections and rejections set forth in the Office Action are addressed below in the order presented therein.

Priority

The Examiner has acknowledged the English language translation of U.S. Provisional Application No. 60/431,173 and the claim of priority to both EP Application 02008761.5 and U.S. Provisional Application No. 60/431,173. However, the Examiner asserts that neither EP Application 02008761.5 filed April 18, 2002 nor U.S. Provisional Application No. 60/431,173 filed December 5, 2002 provide support for either the recited dsRNA of between 15 and 30 nucleotides in length of claim 1, or the recited dsRNA of between 20 and 25 nucleotides in length of claim 93. Applicants have amended independent claim 1 to recite a dsRNA of 21 to 23 nucleotides in length and cancelled claim 93. Support for the amendment to claim 1 can be found on, for example, pages 8-9 and of the English translation of EP Application 02008761.5. Accordingly, acknowledgement that the pending application is entitled to the effective filing date of EP Application 02008761.5, filed April 18, 2002 is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 20 and 21 have been objected to as being in improper dependent form failing to limit the subject matter of the previous claim. Claims 20 and 21 have been cancelled rendering the Examiner's objection moot.

Claims 1, 4-11, 13, 15, 16, 19-23, 92 and 93 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention.

Independent claim 1 stands rejected as the Examiner appears to suggest that a "composition" requires at least two components. While Applicant's attorney notes that the patent literature provides numerous examples of the claimed compositions having one component (see, for example, U.S. Patent No. 4,607,072), Applicant has amended the claims to specifically recite a carrier as part of the composition. Accordingly, the Examiner's rejection of

independent claim 1 and claims depending therefrom under 35 U.S.C. § 112, second paragraph should be withdrawn.

Claims 8, 21, 22 and 23 stand rejected because the Examiner alleges that the scope and meaning of "in a form designed to be applied..." is unclear. Claims 8, 21, 22 and 23 have been cancelled rendering the Examiner's rejection moot. Claims 9, 11, 20 and 21 stand rejected because these claims contain various limitations with insufficient antecedent basis. The antecedent basis problems identified by the Examiner in claims 9 and 11 have been attended to and claims 20-21 have been canceled, rendering the Examiner's rejection of these claims moot.

Claim 9 stands further rejected because claim 9 recites of "inhibitor/antagonist" which the Examiner alleges is unclear. It is noted by Applicants that claim 10 recites similar language. Therefore, claims 9-10 have been amended to recite "inhibitor", and claim 13 has been cancelled, thereby rendering the Examiner's rejections moot.

Claim 11 stands further rejected and has been cancelled rendering the Examiner's rejection moot. Claim 13 was rejected and has been cancelled rendering the Examiner's rejection moot.

35 U.S.C. § 112, First Paragraph

Claims 1, 4-11, 13, 15, 16, 20-23, 92 and 93 stand rejected under 35 U.S.C. § 112, first paragraph for purportedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that Applicants had possession of the claimed invention at the time of filing.

The Examiner rejects claims 1, 4-11, 13, 15, 16, 20-23, 92 and 93 under 35 U.S.C. § 112, first paragraph for a variety of reasons. Applicants respectfully disagree.

Applicants have amended independent claim 1 to clarify that the dsRNA is administered outside the blood-retina barrier. Remarkably, despite being administered systemically, Applicants demonstrate dsRNA overcomes the blood-retinal barrier and silences gene expression in the eye. Applicants' pending claims specifically describe administering a dsRNA of 21-23 nucleotides in length targeting mRNA of a target gene outside the blood-retinal barrier to silence expression of the target gene expressed inside the blood-retinal barrier. The specification and relevant priority documents as originally filed provide support for the claimed method including: multiple examples of suitable target genes, exemplary methods for identifying suitable target genes, exemplary methods for preparing dsRNA, and various methods

administering dsRNA outside the blood-retinal barrier. Moreover, Applicants provide (i) *in vivo* data showing specific silencing of expression of eGFP in the retinal pigment epithelium of transgenic mice through systemic administration, which is outside the blood-retinal barrier, of a 19 nucleotide dsRNA targeting eGFP mRNA, which is expressed inside the blood-retinal barrier (Example 21); (ii) *in vivo* data showing specific silencing of expression of eGFP in the retinal pigment epithelium of transgenic mice through systemic administration, which is outside the blood-retinal barrier, of a 21 nucleotide dsRNA with 3' overhangs targeting eGFP mRNA, which is expressed inside the blood-retinal barrier (Example 1 of EP 02008761.5); (iii) *in vivo* data showing specific silencing of expression of Abca4 in the retinal pigment epithelium of transgenic mice through systemic administration, which is outside the blood-retinal barrier, of a 21 nucleotide dsRNA with 3' overhangs targeting Abca4 mRNA, which is expressed inside the blood-retinal barrier (Example 2 of EP 02008761.5);and (iv) *in vivo* data showing specific silencing of expression of RPE65 in the retinal pigment epithelium of transgenic mice through systemic administration, which is outside the blood-retinal barrier, of a 21 nucleotide dsRNA with 3' overhangs targeting RPE65 mRNA, which is expressed inside the blood-retinal barrier (Example 2 of EP 02008761.5).

The Examiner appears to further suggest that the specification as filed does not provide adequate written description for the genus encompassing "a disorder of the eye" as recited in amended independent claim 1. Applicants respectfully disagree. Applicants provide a substantial list of disorders related to the eye that may be treated using the method of the pending claims (pg. 7, ln. 30 to pg. 8, ln. 8). Each of the maladies identified have at least one known genetic component which leads or predisposes the subject to a disorder of the eye which can be targeted using the claimed method. Additionally, Applicants have provided a substantial list of target genes including accession numbers for retrieval of the genetic sequence of the cDNA (Table, pgs. 55-58). Furthermore, Applicants provide methods for diagnosing eye disorders, culturing the cells of the eye, isolating cDNA, identifying genes that are overexpressed in diseased eyes, determining the genetic sequence of identified genes, preparing siRNA targeting mRNA of the identified genes, and administering the siRNA to the subject, and each of these steps is accompanied by a working example (see, for example, page 3, line 5 to page 5, line 12; page 13, line 24 to page 20, line 6; page 22, lines 4-21, page 24, line 1 to page 28, line 10; page 41, line 28 to page 42, line 5 and each of Examples 1-21). Applicants have not only provided

adequate written description for a vast number of disorders of the eye having a known genetic component, but also provided written description for other disorders of the eye by providing methods for determining the genetic component for any such disorder. Therefore, Applicants' recitation of "a disorder of the eye" is commensurate in scope with the written description provided in the specification as originally filed.

For at least the reasons provided above, Applicants submit that adequate written description is provided in the specification as originally filed. Accordingly, reconsideration and withdrawal of the Examiner's rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

35 U.S.C. § 102

Claims 1, 4, 6-11, 13, 15, 16, 20, 21, 22, 23, 92 and 93 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Publication No. 2002/0165158 to King. The Examiner alleges that King teaches the use of siRNA targeted to PKCβ to treat diabetic retinopathy and other neovascularization disorders of the eye, thus, anticipating the pending claims. Applicants respectfully disagree.

The novelty of Applicant's invention is multi-faceted. First, Applicants provide a very early demonstration that siRNA silences genes *in vivo*; second, Applicants demonstrate that siRNA is effective in silencing genes relevant to disorders of the eye; and third, Applicants demonstrate administering a dsRNA outside the blood-retina barrier to modulate genetic expression inside the eye. Each of these elements alone would be sufficient to support patentability of the presently claimed methods. Cumulatively, they speak to Applicants significant and patentable contributions to the art. It is respectfully submitted that the Examiner is using hindsight in minimizing Applicant's contribution to the art, and establishing a purported *prima facie* case of obviousness.

King fails anticipate the present invention on many fronts. King is simply attempting to mitigate expression of a new target (i.e., PKCβ). Significantly, King fails to provide even one example of a dsRNA being administered. King fails to describe a method in which a dsRNA targeting a gene expressed in the eye is administered to a subject outside the blood-retinal barrier, which mediates inhibition of a target gene inside the eye. King merely describes exogenous expression of PKCβ as contributing to neovascularization and postulates that inhibition of expression of PKCβ may reverse the neovascularization associated with

exogenous expression of PKCβ. King provides a extensive list of potential active agents including antisense, RNAi and antibodies, but fails to show that even a single active agent effectively inhibits PKCβ or the neovascularization associated with exogenous PKCβ expression *in vivo*. Moreover, King fails to show that any such active agent could effectively inhibit PKCβ or the neovascularization associated with exogenous PKCβ expression in the eye following administration of the agent outside the blood-retina barrier. King fails to even mention the blood-retinal barrier, and provides no feasible options for overcoming the barrier. When a physical barrier of the body is described (e.g., transdermal), King specifically notes the need for penetrants appropriate to penetrate the barrier (see paragraph [0190]). Moreover, when King describes administration to the eye and/or retina, King specifically notes that administration is "direct" or "isolated" to the tissue (see paragraphs [0105], [125], and [0194]). Clearly, King does not begin to describe Applicant's presently claimed invention of siRNA traversing the blood-retinal barrier and, in fact, recognizes the limitations of his disclosure.

Furthermore, King cannot be relied upon for providing a method for administering an siRNA outside the blood-retinal barrier to achieve inhibition of expression of a target gene inside the blood-retinal barrier because King fails to provide any working examples of such a method. First and foremost, King fails to provide any specific siRNA species, and fails to show that siRNA targeting PKCβ effectively inhibit expression of PKCβ even *in vitro*. Second, King fails to show that *any substance* described by King can overcome the blood-retinal barrier to inhibit expression of PKCβ inside the eye. Given the unpredictable nature of siRNA and the established difficulties in traversing the blood-retinal barrier, the disclosure of King regarding systemic delivery of siRNA targeting PKCβ and the Examiner's reliance on systemic administration of siRNA should not be considered operative (see MPEP 2121). Accordingly, King fails to anticipate amended independent claim 1, and the Examiner's rejection should be withdrawn. Reconsideration is respectfully requested.

35 U.S.C. § 103

The Examiner rejected claims 1, 4-11, 13, 15, 16, 19-23, 92 and 93 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,814,620 to Robinson et al (hereinafter "Robinson"), U.S. Patent No. 5,498,521 to Dryja et al. (hereinafter "Dryja"), Weber et al. Nucleic Acids Res. 19: 6263-6268 (1991) (hereinafter "Weber"), Epstein et al. Methods: A

Companion to Methods in Enzymology 14:21-33 (1998) (hereinafter "Epstein"), Collins et al. Genomics 13 (3): 698-704 (1992) (hereinafter "Collins") and U.S. Patent Publication No. 2004/0259247 to Tuschl et al. (hereinafter "Tuschl"); Bass Nature 411: 428-429 (2001). The Examiner alleges that: Robinson discloses administration of antisense oligonucleotides to treat diseases associated with the eye; Dryja discloses methods for diagnosing susceptibility to developing ocular disorders and the beta subunit of rod retinal cGMP phosphodiesterase; Weber teaches the full length sequence of cGMP phosphodiesterase; Epstein discloses antisense oligonucleotides inhibitors phosphodiesterase genes; Collins echoes and reinforces Dryja and Epstein; Tuschl discloses a "complete blueprint for the design, synthesis, and use of short interfering, double stranded RNA"; and Bass discloses that siRNA triggers degradation of complementary mRNA. Based on the combined teaching of these references, the Examiner concludes that it would have been obvious to use siRNAs as taught by Tuschl and Bass to inhibit the expression of a target gene to treat disorders of the eye as recited by amended independent claim 1. Applicants respectfully disagree.

Even ignoring the Examiner's need to combine six references to establish a purported *prima facie* case of obviousness, the combined teachings of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass fail to teach or suggest inhibiting expression of a target gene in the eye by administering an siRNA outside the blood-retinal barrier, as required by the claims. At best, Robinson delivers antisense intravitreally, and unequivocally, intravitreal administration is not administration outside the blood-retina barrier. The Examiner purports to rely on Robinson for teaching of administering antisense oligonucleotides systemically to inhibit VEGF expression in the eye (Office Action, pg. 25, 2nd full paragraph), however Robinson fails to provide an actual example of systemically administering even an antisense oligonucleotide outside the blood-retina barrier and none of the supporting references provide any disclosure regarding passage of a dsRNA through the blood-retinal barrier. Therefore, the secondary references fail to cure the deficiencies of Robinson and the combined teachings of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass fail to render the pending claims obvious.

In contrast, Applicants clearly show that dsRNA can pass through the blood-retinal barrier by showing specific silencing of eGFP, Abca4 and RPE65 in retinal pigment epithelium of transgenic mice through systemic administration of dsRNA targeting eGFP, Abca4 and RPE65 mRNA, respectively. Accordingly, Applicants demonstrate that dsRNA can silence

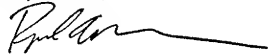
expression of a target gene inside the blood-retinal barrier by delivery of a dsRNA outside the blood-retinal barrier. Based on the teaching of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass as well as what was commonly known at the time of the invention, Applicants results should be considered surprising and unexpected. Thus, any *prima facie* case for obviousness made by the Examiner is effectively rebutted, and the Examiner's rejections based on the combined teachings of Robinson, Dryja, Weber, Epstein, Collins, Tuschl and Bass should be withdrawn. For at least the reasons set-forth above, reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

CONCLUSION

Applicants have timely filed this response. In the event that an additional fee is required for this response, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 50-0436.

Should the Examiner have any questions or comments, or need any additional information from Applicants' attorney, he is invited to contact the undersigned at his convenience.

Respectfully submitted,



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